PATENT
Docket No.: 223002107100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:	Confirmation No.: 5927
Nicholas M. VALIANTE, Jr.	Examiner: Y. S. Chong
Application No.: 10/762,873	Group Art Unit: 1627
Filed: January 21, 2004	
For: USE OF TRYPTANTHRIN COMPOUNDS FOR IMMUNE POTENTIATION	

REPLY BRIEF TO EXAMINER'S ANSWER

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Examiner's Answer in the present case was mailed on April 7, 2010, thus setting a date of June 7, 2010 for this Reply Brief.

Appellant appreciates the acknowledgement of the correctness of the status of claims, the status of amendments, the summary of the claimed subject matter and the grounds of rejection to be reviewed, as well as the claims appendix, as set forth in the Examiner's Answer. Response has been provided herein to what seem to be new arguments raised in the Examiner's Answer.

It is assumed that this Reply Brief will be read in conjunction with the Appeal Brief filed January 28, 2010, and therefore only arguments in response to the Examiner's Answer are presented herein, with all other arguments from the Appeal Brief being incorporated by reference. Although not required, a listing of the claims is attached for the Board's convenience.

There is no *prima facie* case that claims 12-17 and 19 are obvious over Baker in view of Colston

Claims 12-17 and 19 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable for obviousness over Baker et al. (U.S. Patent 5,441,955) [hereinafter "Baker"] in view of Colston et al. (U.S. Patent 7,122,195) [hereinafter "Colston"].

The Examiner's Answer rejects as unpersuasive the Appellant's arguments that one of skill in the art would have had neither a motivation to combine Baker's anti-mycobacterial compounds with Colston's live mycobacterium-containing vaccine compositions, nor a reasonable expectation that the proposed combination would be effective.

Specifically, the Examiner states that the Appellant's argument against combining Baker with Colston "is not persuasive because Appellant is arguing against their own claimed invention. If the composition comprising the combination of the cited prior art is ineffective, why is it that the same composition claimed by the Appellant be enabled?" (Examiner's Answer, page 7, last paragraph.) The Examiner points to paragraphs [0111]-[0121] of the instant application as allegedly disclosing that vaccines encompassed by the claims may include live viral and bacterial immunogens. (Examiner's Answer, page 8, second paragraph.)

The Examiner's position relies on a mischaracterization of the Appellant's invention, which is clearly distinguishable from the proposed combination of Baker and Colston. The claimed invention contains an antigen and a tryptanthrin compound, but does not contain live mycobacterial

cells, which is an essential part of Colston's composition. The Appellant's invention is thus not plagued with the problems one of skill in the art would have expected when combining Baker's compounds with Colston's vaccine composition.

While the open transitional phrase 'comprising' in the instant claims may theoretically encompass the combination of Baker's compounds and Colston's vaccine, the references themselves provide sufficient guidance to prevent a person of ordinary skill from making the proposed combination. This is especially true since the present specification teaches that the tryptanthrin compound is itself an immune potentiator, so it replaces the live mycobacterium relied upon in Colston's compositions to potentiate the immune response. Thus, the proposed combination would be inappropriate in view of the specification and the teachings of the cited references.

With respect to the comment on page 8 of the Examiner's Answer that Appellants have not provided factual evidence that a tryptanthrin compound would, in fact, render Colston's vaccine ineffective, Appellant's respectfully submit that such evidence is neither required nor relevant to the enquiry of what a person of skill in the art would have believed based on the disclosures of the cited documents at the time of the invention. As explained in the Appellant's Appeal Brief, Baker's disclosure that its compounds are useful to kill mycobacteria provides a clear, if implicit, teaching away from mixing such compounds with Colston's vaccine compositions, which require a live mycobacterium to be effective. One of skill in the art would have reasonably concluded, based on the respective disclosures of Baker and Colston, that the proposed combination was fundamentally incompatible.

Moreover, the conclusion on page 8 of the Examiner's Answer that one of ordinary skill in the art would have had a reasonable expectation of success "even if the viral or bacteria immunogen would be killed, it matters little since most vaccines use completely killed or attenuated (weakened) immunogens" disregards the express teachings of Colston that persistence of the live mycobacterium in the host is necessary for their vaccine composition to work. See Colston, col.15, line 63 to col. 16, line 2.

The Examiner further rejects the Appellant's argument that nothing in the cited art would motivate one of skill in the art to practice the invention as claimed, nor provide a basis to conclude that the tryptanthrin compound of Baker would *necessarily* be present in an amount effective to promote an enhanced immune response even if it were for some reason physically admixed with a vaccine composition.

In particular, the Examiner's Answer states that this is not persuasive because "the instant claims do not recite a particular dosage range that will enable the tryptanthrin compound to promote an enhanced immune response to an antigen. Therefore, interpreting the claim broadly, any dosage amount of tryptanthrin will obviously have the same properties. Furthermore, the specification is not clear on what the metes and bounds are regarding the dosage amount of tryptanthrin to promote an enhanced immune response to an antigen." (Examiner's Answer, pages 9-10.)

The Examiner's position ignores the clear limitations in independent claim 12, which require that the tryptanthrin compound adjuvant is present in the immunogenic composition in an amount effective to provide an enhanced immune response to the antigen, where an "enhanced immune response" is determined relative to the response provided without the tryptanthrin compound

adjuvant. Thus, the plain language of the claim clearly provides a functional way to determine the amount of the tryptanthrin compound adjuvant that constitutes an "effective amount," as claimed.

Appellant's respectfully submit that whether the broad dosage range disclosed by Baker, encompassing a total daily dose of from 0.001 to 1000 mg/kg body weight (i.e., over 6-orders of magnitude), overlaps with the "effective amount" of the Appellant's invention is irrelevant to the question of whether one of skill in the art would have had a motivation to combine Baker's compounds with Colston's compositions in the first place. Moreover, the disclosed range provides no guidance for the selection of an appropriate amount to enhance an immune response to an antigen, or any basis to reasonably suggest to one of skill in the art that an amount exists whereby the tryptanthrin compound will be capable of functioning as an adjuvant, as claimed.

Finally, in response to the Examiner's contention that the Appellant's arguments rely on attacking the references to Baker and Colston separately, Appellants respectfully disagree. Appellants respectfully submit that the arguments presented clearly explain why one of skill in the art would have expected the Examiner's proposed combination of Baker's compounds with Colston's vaccine compositions to be ineffective, and therefore would have had neither a motivation nor a reasonable expectation of success based on the proposed combination.

The Examiner's position that the present invention would have been obvious to one of skill in the art in view of the cited references improperly relies on hindsight reasoning based on the Appellant's discovery. Accordingly, the Office has failed to establish a *prima facie* case of obviousness of the claimed invention over Baker in view of Colston.

Conclusion

The present invention provides an immunogenic pharmaceutical composition comprising an antigen and a tryptanthrin compound adjuvant in an amount effective to provide an enhanced immune response to the antigen relative to the response provided without the tryptanthrin compound adjuvant.

The cited art fails to provide a *prima facie* case of obviousness for the claimed invention over Baker in view of Colston. Few of Appellant's arguments regarding the lack of a motivation to combine the cited documents and the lack of a reasonable expectation of success have been addressed on the record. Moreover, even if a *prima facie* case for obviousness were established, unrebutted evidence favoring a conclusion of nonobviousness has been disregarded by the Office.

Appellants respectfully request that the rejections be withdrawn and claims 12-17 and 19 be passed to issue on an expedited basis.

An Oral Hearing is requested.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Reply Brief, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

Dated: June 7, 2010

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CLAIMS APPENDIX

Complete Listing of the Claims, including Claims Involved in the Appeal of Application Serial 10/762,873:

1. (withdrawn): A method of enhancing an immune response in a subject to an antigen, the method comprising administering to a subject an immunogenic pharmaceutical composition comprising the antigen and a tryptanthrin compound adjuvant in an amount effect to provide an enhanced immune response to the antigen relative to the response provided without the tryptanthrin compound adjuvant.

2. (withdrawn): The method of claim 1, wherein the antigen is derived from a bacterial, parasitic, viral, or fungal pathogen.

3. (withdrawn): The method of claim 2 wherein the bacterial pathogen is selected from the group consisting of diphtheria, staphylococcus, cholera, tuberculosis, tetanus, streptococcus pneumoniae, streptococcus agalacitiae, streptococcus pyogenes, pertussis, Neisseria meningitis, Neisseria gonorrheae, chlamydia, Helicobacter pylori, and Hemophilius influenza type B.

4. (withdrawn): The method of claim 2 wherein the viral pathogen is selected from the group consisting of viral meningitis, rhinovirus, influenza, respiratory syncytial virus, parainfluenza virus, rotavirus, tick borne encephalitis virus, coronaviridae, rhabodoviridiae, VZV, EBV, CMV, HIV, HPV, HSV, HAV, HBV, HCV, and SARS.

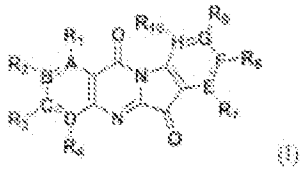
5. (withdrawn): The method of claim 2 wherein the parasitic pathogen is selected from the group consisting of Plasmodium falciparum, Plasmodium ovate, Plasmodium malariae, and P. vivax.

6. (withdrawn): The method of claim 2, wherein the antigen is associated with a disease selected from the group consisting of BCG, cholera, plague, typhoid, hepatitis B infection, influenza, inactivated polio, rabies, measles, mumps, rubella, oral polio, yellow fever, tetanus,

diphtheria, hemophilus influenzae b, meningococcus infection, tick borne encephalitis, SARS, HCV, HIV, and pneumococcus infection.

7. (withdrawn): The method of claim 1 wherein the immune response is the cellular production of one or more cytokines.

8. (withdrawn): The method of claim 1 wherein the tryptanthrin compound is a compound of Formula (I):



(I)

wherein

A, B, C, D, E, F, G, and H are independently selected from carbon and nitrogen, or A and B and/or C and D can he taken together to be nitrogen or sulfur; R_1, R_2, R_3, R_4, R_8, and R_{10} are independently selected from the group consisting of hydrogen, halogen, loweralkyl, alkyl, substituted alkyl, cycloalkyl, heterocyclyl, alkylheterocyclyl, substituted heterocyclyl, substituted alkenyl, amino, (substituted alkyl)(alkyl)amino, imino, halologweralkyl, hydroxy, alkoxy, substituted alkoxy, hydroxyalkylthio, nitro, alkylsulfonyl, N-alkylsulfonamide, arylalkyl, arylalkylaryl, arylaryl, aryloxy, arylamino, acylamino, acyloxyamino, alkylaminoacylamino, alkylaminosulfonylamino, alkylamino, alkenylamino, dialkylamino, alkoxyalkylamino, alkoxyalkylheterocyclyl, mercaptoalkoxyalkyl, cyano, formyl, -$COOR_{11}$ wherein R_{11} is hydrogen, loweralkyl, aryl, heterocyclyl, monosaccharide or disaccharide, and -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently selected from hydrogen, loweralkyl, aryl, heterocyclyl, saccharide, peptide and amino acid residues; or R_2 and R_3 taken together form a six membered aromatic ring;

R_7 and R_9 are independently selected from hydrogen, halogen, loweralkyl, halologweralkyl, cycloalkyl, heterocyclyl, substituted heterocyclyl or heterocyclylalkyl; and

R_1, R_2, R_3, R_4, R_7, R_8, R_9, and R_{10} are absent when the ring atom to which they would otherwise be bonded is sulfur or double-bonded nitrogen; or

a pharmaceutically acceptable salt,

provided that R_1, R_2, R_3, R_4, R_7, R_8, R_9, and R_{10} are not all hydrogen when A, B, C, D, E, F, and H are carbon.

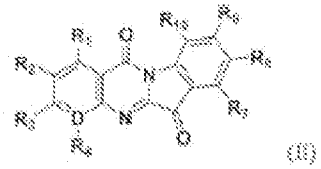
9. (withdrawn): The method of claim 8,

wherein

A, B, C, D, E, F, G, and H are independently selected from carbon and nitrogen;

R_1, R_2, R_3, R_4, R_8 and R_{10} are independently selected from the group consisting of hydrogen, halogen, loweralkyl, alkyl, substituted alkyl, heterocyclyl, substituted heterocyclyl, substituted alkenyl, (substituted alkyl)(alkyl)amino, halologweralkyl, hydroxy, alkoxy, substituted alkoxy, hydroxyalkylthio, nitro, N-alkylsulfonamide, cyano, -$COOR_{11}$ wherein R_{11} is hydrogen, loweralkyl, aryl, heterocyclyl, monosaccharide or disaccharide, and -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently selected from hydrogen, loweralkyl, aryl, heterocyclyl, saccharide, peptide and amino acid residues.

10. (withdrawn): The method of claim 1 wherein the tryptanthrin compound is a compound of Formula (II):



(II)

wherein

D is carbon or nitrogen, and R_4 is absent when D is N;

R_1 is hydrogen, halogen, or loweralkyl;

R_2 is hydrogen or halogen;

R_3 is hydrogen, halogen, heterocyclyl, substituted heterocyclyl, (substituted alkyl)(alkyl)amino, or hydroxyalkylthio;

R_4 is hydrogen, halogen, alkoxy, substituted alkoxy, or hydroxy;

R_7 is hydrogen or halologweralkyl;

R_8 is hydrogen, halogen, substituted alkoxy, halololoweralkyl, nitro, N-alkylsulfonamide, substituted alkenyl, substituted alkyl, $COOR_{11}$ wherein R_{11} is loweralkyl, or $-CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently hydrogen or loweralkyl;

R_9 is hydrogen; and

R_{10} is hydrogen, halogen, or loweralkyl;

or a pharmaceutically acceptable salt thereof.

11. (withdrawn): The method of claim 1, wherein the tryptanthrin compound is selected from the group consisting of:

8-nitroindolo[2,1-b]quinazoline-6,12-dione,

3,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

10-fluoroindolo[2,1-b]quinazoline-6,12-dione,

1,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-l-methylindolo[2,1-b]quinazoline-6,12-dione,

8,10-difluoroindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-l-fluoro-8-iodoindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-1-chloro-8-iodoindolo- [2,1-b]quinazoline-6,12-dionc,

2,4-dibromo-l-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-2-iodoindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-3-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-4-hydroxyindolo[2,1-b]quinazoline-6,12-dione,

N-ethyl-4-(methyloxy)-6,12-dioxo-6,12-dihydroindolo[2,1-b]quinazoline-8-carboxamide,

3-fluoro-8-[(trifluoromethyl)oxy]indolo[2,1-b]quinazoline-6,12-dione,

3-[(2-hydroxyethyl)thio]-8-[(trifluoromethyl)oxy]indolo[2,1-b]quinazoline-6,12-dione,

pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-fluoropyrido[2',3':4,5]pyrimido[1,2-a] indole-5,11-dione,

9-bromopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-chloropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-iodopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

ethyl 5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-carboxylate,

N-octyl-5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-sulfonamide,

10-(trifluoromethyl)pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

(5E)-6-(5,11-dioxo-5,11 dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hex-5-enyl acetate,

6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hexyl dihydrogen phosphate, and

9-[(trifluoromethyl)oxy]pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

or a pharmaceutically acceptable salt thereof.

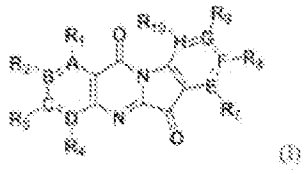
12. (previously presented): An immunogenic pharmaceutical composition comprising an antigen and a tryptanthrin compound adjuvant in an amount effective to provide an enhanced immune response to the antigen relative to the response provided without the tryptanthrin compound adjuvant.

13. (original): The composition of claim 12, further comprising an aqueous carrier.

14. (previously presented): The composition of claim 12, wherein the antigen is associated with a disease selected from the group consisting of cholera, plague, typhoid, hepatitis B infection, influenza, inactivated polio, rabies, measles, mumps, rubella, oral polio, yellow fever, tetanus, diphtheria, hemophilus influenzae b, meningococcus infection, tick borne encephalitis, SARS, HCV, HIV, and pneumococcus infection.

15. (previously presented): The composition of claim 12, wherein the tryptanthrin compound enhances an immune response to the antigen and the immune response is the cellular production of one or more cytokines.

16. (original): The composition of claim 12, wherein the tryptanthrin compound is a compound of Formula I:



(I)

wherein

A, B, C, D, E, F, G, and H are independently selected from carbon and nitrogen, or A and B and/or C and D can be taken together to be nitrogen or sulfur;

R_1, R_2, R_3, R_4, R_8, and R_{10} are independently selected from the group consisting of hydrogen, halogen, loweralkyl, alkyl, substituted alkyl, cycloalkyl, heterocyclyl, alkylheterocyclyl, substituted heterocyclyl, substituted alkenyl, amino, (substituted alkyl)(alkyl)amino, imino, halologweralkyl, hydroxy, alkoxy, substituted alkoxy, hydroxyalkylthio, nitro, alkylsulfonyl, N-alkylsulfonamide, arylalkyl, arylalkylaryl, arylaryl, aryloxy, arylamino, acylamino, acyloxyamino, alkylaminoacylamino, alkylaminosulfonylamino, alkylamino, alkenylamino, dialkylamino, alkoxyalkylamino, alkoxyalkylheterocyclyl, mercaptoalkoxyalkyl, cyano, formyl, -$COOR_{11}$ wherein R_{11} is hydrogen, loweralkyl, aryl, heterocyclyl, monosaccharide or disaccharide, and -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently selected from hydrogen, loweralkyl, aryl, heterocyclyl, saccharide, peptide and amino acid residues; or R_2 and R_3 taken together form a six membered aromatic ring;

R_7 and R_9 are independently selected from hydrogen, halogen, loweralkyl, halologweralkyl, cycloalkyl, heterocyclyl, substituted heterocyclyl or heterocyclylalkyl; and

R_1, R_2, R_3, R_4, R_7, R_8, R_9, and R_{10} are absent when the ring atom to which they would otherwise be bonded is sulfur or double-bonded nitrogen; or

a pharmaceutically acceptable salt thereof,

provided that R_1, R_2, R_3, R_4, R_7, R_8, R_9, and R_{10} are not all hydrogen when A, B, C, D, E, F, and H are carbon.

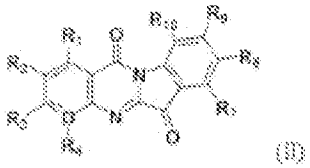
17. (original): The composition of claim 16,

wherein

A, B, C, D, E, F, G, and H are independently selected from carbon and nitrogen;

R_1, R_2, R_3, R_4, R_8 and R_{10} are independently selected from the group consisting of hydrogen, halogen, loweralkyl, alkyl, substituted alkyl, heterocyclyl, substituted heterocyclyl, substituted alkenyl, (substituted alkyl)(alkyl)amino, halologweralkyl, hydroxy, alkoxy, substituted alkoxy, hydroxyalkylthio, nitro, N-alkylsulfonamide, cyano, -$COOR_{11}$ wherein R_{11} is hydrogen, loweralkyl, aryl, heterocyclyl, monosaccharide or disaccharide, and -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently selected from hydrogen, loweralkyl, aryl, heterocyclyl, saccharide, peptide and amino acid residues.

18. (withdrawn): The composition of claim 12, wherein the tryptanthrin compound is a compound of Formula II:



(II)

wherein

D is carbon or nitrogen, and R_4 is absent when D is N;

R_1 is hydrogen, halogen, or loweralkyl;

R_2 is hydrogen or halogen;

R_3 is hydrogen, halogen, heterocyclyl, substituted heterocyclyl, (substituted alkyl)(alkyl)amino, or hydroxyalkylthio;

R_4 is hydrogen, halogen, alkoxy, substituted alkoxy, or hydroxy;

R_7 is hydrogen or halologweralkyl;

R_8 is hydrogen, halogen, substituted alkoxy, halologweralkyl, nitro, N-alkylsulfonamide, substituted alkenyl, substituted alkyl, $COOR_{11}$ wherein R_{11} is loweralkyl, or -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently hydrogen or loweralkyl;

R_9 is hydrogen; and

R_{10} is hydrogen, halogen, or loweralkyl;

or a pharmaceutically acceptable salt thereof.

19. (original): The composition of claim 12, wherein the tryptanthrin compound is selected from the group consisting of

8-nitroindolo[2,1-b]quinazoline-6,l-2-dione,

3,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

10-fluoroindolo[2,1-b]quinazoline-6,12-dione,

1,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-l-methylindolo[2,1-b]quinazoline-6,12-dione,

8,10-difluoroindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-l-fluoro-8-iodoindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-1-chloro-8-iodoindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-1-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-2-iodoindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-3-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-4-hydroxyindolo[2,1-b]quinazoline-6,12-dione,

N-ethyl-4-(methyloxy)-6,12-dioxo-6,12-dihydroindolo[2,1-b]quinazoline-8-carboxamide,

3-fluoro-8-[(trifluoromethyl)oxy]indolo[2,1-b]quinazoline-6, 12-dione,

3-[(2-hydroxyethyl)thio]-8-[(tri fluoromethyl)oxy]indolo[2,1-b]quinazoline-6,12-dione,

pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-fluoropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-bromopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-chloropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-iodopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

ethyl 5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-carboxylate,

N-octyl-5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-sulfonamide,

10-(trifluoromethyl)pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

(5E)-6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hex-5-enyl acetate,

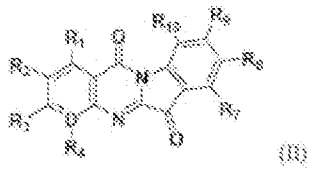
6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hexyl dihydrogen phosphate, and

9-[(trifluoromethyl)oxy]pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

or a pharmaceutically acceptable salt thereof.

20. (withdrawn): A method of immunotherapy for the treatment of cancer, the method comprising administering to a subject an immunostimulatory effective amount of a tryptanthrin derivative.

21. (withdrawn): The method of claim 20, wherein the tryptanthrin derivative is a compound of Formula II:



(II)

wherein

D is carbon or nitrogen, and R_4 is absent when D is N;

R_1 is hydrogen, halogen, or loweralkyl;

R_2 is hydrogen or halogen;

R_3 is hydrogen, halogen, heterocyclyl, substituted heterocyclyl, (substituted alkyl)(alkyl)amino, or hydroxyalkylthio;

R_4 is hydrogen, halogen, alkoxy, substituted alkoxy, or hydroxy;

R_7 is hydrogen or haloloweralkyl;

R_8 is hydrogen, halogen, substituted alkoxy, haloloweralkyl, nitro, N-alkylsulfonamide, substituted alkenyl, substituted alkyl, $COOR_{11}$, wherein R_{11} is loweralkyl, or $-CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently hydrogen or loweralkyl;

R_9 is hydrogen; and

R_{10} is hydrogen, halogen, or loweralkyl;

or a pharmaceutically acceptable salt thereof.

22. (withdrawn): The method of claim 20, wherein the tryptanthrin derivative is selected from the group consisting of

8-nitroindolo[2,1-b]quinazoline-6,12-dione,

3,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

10-fluoroindolo[2,1-b]quinazoline-6,12-dione,

1,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-l-methylindolo[2,1-b]quinazoline-6,12-dione,

8,10-difluoroindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-l-fluoro-8-iodoindolo[2,l-b]quinazoline-6,12-dione,

2,4-dibromo-l-chloro-8-iodoindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-1-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-2-iodoindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-3-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-4-hydroxyindolo[2,1-b]quinazoline-6,12-dione,

N-ethyl-4-(methyloxy)-6,12-dioxo-6,12-dihydroindolo[2,1-b]quinazoline-8-carboxamide,

3-fluoro-8-[(trifluoromethyl)oxy]indolo[2, 1-b]quinazoline-6,12-dione,

3-[(2-hydroxycthyl)thio]-8-[(trifluoromethyl)oxy]indolo[2,1-b]quinazoline-6,12-dione,

pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-fluoropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-bromopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-chloropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-iodopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

ethyl 5,11-dioxo-511-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-carboxylate,

N-octyl-5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-sulfonamide,

10-(trifluoromethyl)pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

(5E)-6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hex-5-enyl acetate,

6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hexyl dihydrogen phosphate, and

9-[(trifluoromethyl)oxy]pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

or a pharmaceutically acceptable salt thereof.

23.-31. (canceled)